41. (New) The method of claim 40, wherein the domain that binds to a receptor expressed on a cancer cell is an apoptosis-promoting domain.

42. (New) The method of claim 41, wherein the apoptosis-promoting domain inhibits STAT3 phosphorylation in the cancer cell bearing the receptor to which the apoptosis-promoting domain binds.

43. (New) The method of claim 9, wherein SEQ ID NO. 1 comprises one or more conservative amino acid substitutions.

44. (New) The method of claim 10, wherein said truncated prolactin sequence comprises one or more conservative amino acid substitutions.

## REMARKS

### I. Status of the Claims

Claims 1-10, 22, 24, and 25 are pending following applicants' election of Group I in their paper of April 8, 2002. None of the elected claims have been cancelled. Claims 1-10, 22, 24, and 25 have been amended. Claims 28-44 have been added.

The amended claims do not introduce new matter. The claims have been amended solely to clarify certain aspects of the invention and to make certain claims more grammatically correct. None of the newly-added claims (claims 28-44) introduce new matter. The new claims are directed to specific embodiments of the present invention.

### II. Summary of the Present Invention

Applicants' present invention relates to a method of targeting and destroying cancer cells. Applicants' method entails administering to an individual possessing cancer cells, a bi-functional protein that induces apoptosis

of cancer cells while simultaneously inducing an immune response that targets those particular cells.

The bi-functional protein comprises a mutated prolactin protein (the "prolactin-antagonist") that binds to prolactin receptors which are overexpressed on the surface of cancer cells, particularly on the surfaces of breast and prostate cancer cells. The mutated prolactin protein reverses the effects of endogenous, wild-type prolactin, by preventing the inhibition of apoptosis. Accordingly, the mutated prolactin protein alters a normal function associated with the prolactin receptor. Wild-type prolactin, when it binds to a prolactin receptor, inhibits apoptopic cell death of that cell. However, the mutated version *induces* apoptosis. The bi-functional protein further comprises an "immunomodulator" protein, such as an interleukin or an interferon, which invokes an immune response directed at cells to which the bi-functional protein is bound.

Accordingly, applicants' invention kills cancer cells in two ways: (i) by making cancer cells to which the bi-functional protein is bound more susceptible to apoptosis, and (ii) directing the host's immune system to those same cells.

## III. Summary of the Office Action

The examiner rejected the claims for the following reasons:

(i) **Claims 1-10, 22, 24, and 25** are rejected under 35 U.S.C. § 112, second paragraph: The examiner contends that the terms, "receptor-antagonizing domain," "positive immunomodulator domain," and "effective" are indefinite and vague. The examiner also holds that the term "conservative variant" in claims 9 and 10 also is unclear.

(ii) **Claims 1, 10, 22, 24, and 25** are rejected under 35 U.S.C. § 112, first paragraph: The examiner alleges that the specification does not enable a method of treating any cancer, nor does it enable a method of treating cancer using a protein containing IL-12 or IFNγ, and that there is no support in the

specification for a method of treating cancer which uses a truncated form or conservative variant of SEQ ID NO. 1.

(iii) **Claims 1, 3, 4, and 5** are rejected under 35 U.S.C. § 102(b): The examiner believes that Lode *et al.*, *Proc. Natl. Acad. Sci. USA*, 96(4), pp1591-1596, 1999, anticipates these claims because Lode *et al.* allegedly teaches a method of treating tumors using a protein containing an antagonizing domain and an immunomodulator region.

The examiner also maintains that claim 5 is anticipated by Gillies *et al.*, J. Immuno., 160(12), pp6195-203, 1998, because Gillies *et al.* allegedly teaches a "method of treating cancer comprising administering to a patient an amount of a protein having a receptor-antagonizing domain, wherein the positive immunomodulator is an IL-12."

(iv) **Claim 24** is rejected under 35 U.S.C. § 103(a): The examiner asserts that claim 24 is obvious over the combination of Lode *et al.* in view of Bulfone-Paus *et al.*, Transplantation, 69(7), pp1386-91, 2000. In light of these references, the examiner believes that it would have been obvious to make the inventive protein composition because there was motivation to use an apoptosis promoting domain in place of a receptor-antagonizing domain.

Applicants respectfully disagree and traverse each rejection for the reasons that follow below.

**(i) Claims 1-10, 22, 24, and 25 are not indefinite**

The examiner contends that the terms, "receptor-antagonizing domain," "positive immunomodulator domain," "effective" and "conservative variant" are indefinite and vague. Applicants disagree and traverse the rejection.

Section 608.01(o) of the MANUAL OF PATENT EXAMINING PROCEDURE, states that:

*"The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification with clear disclosure as to its import . . . A term used in the claims may be given a special meaning in the description"* (emphasis added).

Applicants' specification is clear as to the definition of a "receptor-antagonizing domain." *See*, the section at page 10 of the specification, entitled, "***Receptor-antagonizing domain***." There, applicants explain that a fusion protein containing a domain that is specific to a receptor expressed on a cancer cell will be able to specifically target cancer-cell-containing tissues. The word "import" in MPEP Section 608.01(o) refers to the quality of something, that gives it special meaning or value." Accordingly, Applicants signify the importance of the "receptor-antagonizing domain," in paragraphs 35 and 36 by elaborating that a "domain" that targets a particular receptor "is a receptor-antagonizing domain," which "binds to and antagonizes its cognate receptor." Continuing, when the receptor-antagonizing domain is designed to bind to a prolactin receptor, *i.e.*, when the receptor-antagonizing domain is a "prolactin antagonist," then "the normal endocrine function of prolactin will be disrupted," and consequently, apoptosis results.

Accordingly, having read the specification, the skilled artisan would know that a receptor-antagonizing domain of the present invention is one that targets a receptor expressed on a cancer cell and brings about some detrimental change to that cell. Contrary to the examiner's assertion, then, the skilled artisan would not assume that "virtually any protein that antagonizes a receptor" can be used in the context of the present invention.

In similar fashion, applicants defined a "positive immunomodulator domain" at page 9, paragraph 31, to be that portion of the inventive protein which induces the patient's own immune system to respond specifically against the diseased tissue. See also the subsection entitled, "***Positive immunomodulator domain***" at page 18. There, applicants elaborate that immunomodulator domains support a tumor-directed positive immune response,

and that examples include cytokines that can recruit T lymphocytes to the tumor, thereby inducing tumor specific T lymphocyte cytotoxicity at the malignant tissue. A cytokine is generally understood to be any of several regulatory proteins, such as the interleukins and lymphokines, that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response. *See*, THE AMERICAN HERITAGE DICTIONARY, 4th Edition, Exhibit A.

The examiner, however, rejects the meaning attributed to this term as being vague and indefinite because "a positive immunomodulatory response can at times mean a decrease in immune cell response." See point 4, at page 2 of the Office Action. The examiner's rationale has no bearing on any element recited in method claim 1. Claim 1 recites a "method for treating cancer" by administering to an individual, a protein having a receptor-antagonizing domain and a positive immunomodulator domain. While applicants state that the immunomodulator domain "is one that augments an immune response, preferably enhancing the immune response against an abnormal cell," (page 9, paragraph 30), there is no requirement in claim 1 that the positive immunomodulator domain is associated with a particular immune response. There is no requirement in the claim that the immunomodulator domain *increase* the individual's immune cell response. The specification defines suitable immunomodulators as cytokines, which induce a variety of immunological pathways.

Accordingly, from reading the specification, the skilled artisan would understand that a "positive immunomodulator domain" is one that brings about an immune response that is directed to a particular cancer cell. It is well within the knowledge of the skilled artisan what molecules can function as immunomodulators, but even so, applicants explicitly teach that suitable immunomodulators include IL-2, IL-12 and any of a number of interferons. See paragraphs 54 to 56 at pages 18 and 19 of the specification.

The examiner also believes that the word "effective" is unclear, because the examiner does not understand "how treatment of cancer using the protein

containing a receptor-antagonizing domain and an immunomodulator domain, is to effect the end result." See point 4, at page 2 of the Office Action.

With all.due respect, a premise of the present invention is to use a protein that comprises a receptor-antagonizing domain and an immunomodulator domain to induce an immune response that is targeted to cancer cells. In defining the terms "receptor-antagonizing domain" and "immunomodulator domain" in the specification, applicants have explained that an "effect" of the receptor-antagonizing domain is to bind to a receptor present on a cancer cell and alter the normal biochemical pathway associated with that receptor. Accordingly, the "effect" of the accompanying immunomodulator domain is to elicit an immune response directed to that particular cell. Nevertheless, applicants have deleted recitation of this word from the claims.

The examiner also contends that the phrase "conservative variant," recited in claims 9 and 10, is indefinite, because it is allegedly "unclear as to what this variation or modification would be, that would 1) constitute a conserved modification, and 2) what it is exactly." See point 5, at page 2 of the Office Action.

Applicants respectfully disagree and traverse the rejection. Applicants clearly explain and define what they mean by the term "conservative variant" throughout the specification. See for instance, paragraphs 42 to 46 at pages 14 and 15 of the application. There, applicants state that "one aspect of the invention contemplates conservative variants of PRL that are characterized by the presence of a relatively small side-chain amino acid (i.e. Gly) at a specific position, such that substituting the small side-chain amino acid for a bulky side-chain amino acid will result in an antagonistic form of the protein.

Applicants further elaborate that conservative variants "generally conserve the overall molecular structure of the protein domains," and that amino acid substitutions, that are conservative in nature may be made, for instance, on the

basis of "similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved."

Applicants explicitly recite, at paragraph 45 at page 15, specific types of substitutions that can be made to generate a "conservative variant" of the present invention:

> *"For example: (a) nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; (b) polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; (c) positively charged (basic) amino acids include arginine, lysine, and histidine; and (d) negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Substitutions typically may be made within groups (a)-(d). In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices. Similarly, certain amino acids, such as alanine, cysteine, leucine, methionine, glutamic acid, glutamine, histidine and lysine are more commonly found in α-helices, while valine, isoleucine, phenylalanine, tyrosine, tryptophan and threonine are more commonly found in -pleated sheets. Glycine, serine, aspartic acid, asparagine, and proline are commonly found in turns. Some preferred substitutions may be made among the following groups: (i) S and T; (ii) P and G; and (iii) A, V, L and I. Given the known genetic code, and recombinant and synthetic DNA techniques, the skilled scientist readily can construct DNAs encoding the conservative amino acid variants."*

Furthermore, applicants teach that a truncated receptor-antagonizing domain may also constitute a "conservative variant." They explain that "truncations may be made from the N- or C-terminus, but generally do not entail deleting more than about 30% of the native molecule. More preferably, less than about 20%, and most preferably, less than about 10%, of the native molecule is deleted." See paragraph 46 at page 15 of the specification.

Accordingly, the present invention also contemplates conservative variants which are truncated receptor-antagonizing domains that contain conservative amino acid substitutions.

Even without these explicit teachings, the skilled artisan is well aware of what the term "conservative variant" means and what the word "conservative" means with respect to modified proteins. The On-line Medical Dictionary, for instance, (http://cancerweb.ncl.ac.uk/omd/index.html) contains over 46,000 definitions, including one for "conservative substitution," (Exhibit B). The definition posted as of November 18, 1997, on that website states that a "conservative substitution" refers to "a substitution of one amino acid with another with generally similar properties (size, hydrophobicity, etc), such that the overall functioning is likely not to be seriously affected." Furthermore, the art prior to March 2000, the date when the priority document for the present application was filed, is replete with the use of such a term.

Thus, the examiner's claim that the specification is"unclear as to what this variation or modification would be, that would 1) constitute a conserved modification, and 2) what it is exactly" is unfounded.

As elaborated above, applicants have explained what types of variations or modifications constitute a "conserved modification" and are explicit as to what exact types of modifications are encompassed by the present invention. Nevertheless, applicants have replaced the phrase "conservative variant" recited in the claims with the phrase "conservative amino acid substitution."

Accordingly, claims 9 and 10 are not indefinite and applicants respectfully request that the examiner withdraw this rejection.

(ii) **Claims 1, 10, 22, 24, and 25 are enabled**

Claims 1, 10, 22, 24, and 25 are rejected under 35 U.S.C. § 112, first paragraph, because the examiner alleges that the specification does not enable a method of treating any cancer; does not enable a method of treating cancer

using a protein containing IL-12 or IFNγ; and does not support a method of treating cancer using a truncated form or conservative variant of SEQ ID NO. 1.

The examiner admits, however, that the present specification is enabling for "[1] a method of treating cancer cells that over express prolactin receptors, [2] a method of treating cancer using a protein containing a prolactin receptor antagonizing domain and an immunomodulator region of IL-2, and [3] a method of treat [sic] cancer using a protein having an amino acid sequence of SEQ ID NO. 1."

Nevertheless, the examiner holds that the specification is "virtually silent with regard to any other limitations" and, consequently, the skilled artisan would be "forced into undue experimentation in order to practice the claimed invention using all of the limitations set forth in the instant application."

According to the examiner, there is a "high" quantity of experimentation associated with determining which cancers can be treated with the inventive proteins; as well as with determining the effects of replacing IL-2 with IL-12 or IFNγ, and the effects of using a truncated or conservative variant of SEQ ID NO. 1. To the examiner, the level of experimentation is high because "cancers all have different etiologies and characteristics which require different methods and forms of treatment."

Applicants respectfully disagree and traverse the rejection.

As applicants elaborated above, one aspect of the present invention is the use of a bi-functional protein comprising a mutated prolactin-antagonist that binds to prolactin receptors that are overexpressed on the surface of cancer cells, to destroy cancer cells.

The examiner states that the specification does not enable a method of treating any cancer. However, applicants invention is directed to targeting cancer cells that overexpress a receptor to which the inventive receptor-antagonizing domain binds and elicits both apoptosis and an immune response.

**So long as the cancer cell overexpresses such a receptor then that type of cancer is treatable using the bi-functional agents of the present invention**. To this end, applicants draw the examiner's attention to subsection VIII, entitled "Summary and Conclusions" at page 252, second column of Bole-Feysot *et al.*, Endocrine Reviews, 19(3): 225-268, 1998, (Exhibit C). There, Bole-Feysot *et al.* states "[A] number of disease states, including the growth of different forms of cancer as well as various automimmune diseases, appear to be related to an overproduction of PRL [prolactin receptor]."

The skilled artisan would know that the use of a bi-functional molecule that binds to a receptor which is overexpressed in a cancer cell, as taught by applicants, would be useful in destroying and directing the host's immune response to particular cancer cells. The skilled artisan, having read the present specification, would understand that it is possible to design a bi-functional molecule so that it comprises a receptor-antagonizing domain which binds to a receptor overexpressed in cancer cells in the manner prescribed by the present invention. Indeed, applicants teach how to use a prolactin-antagonist to bind to prolactin receptors that are overexpressed in cancer cells. Applicants also teach that breast and prostate cancer cells overexpress the prolactin receptor. See, for instance, the specification at pages 2 and 3. In addition, applicants also teach that mutated bovine and human growth hormones, in addition to prolactin, can be anatagonists that function in the same way as the prolactin-antagonist. See paragraph 49 at page 17 of the specification ("Thus, antagonists such as GHA [growth hormone antagonists] are contemplated by the invention").

It is well within the purview of the skilled artisan to design, in appropriate fashion, a receptor-binding antagonist that functions in the same manner as the present invention. In similar fashion, it is well within the skilled artisan's capabilities to replace the IL-2 immunomodulatory domain of the bi-functional molecule with IL-12 or IFNγ. Applicants teach at paragraphs 55 and 56 at page 19 of the specification that

> *"In addition to IL-2, the invention contemplates other molecules, including additional **cytokines**, having these or similar properties. For example, **IL-12** can represent the positive immunomodulator domain. . . . The invention also includes conservative variants (as detailed above) of the aforementioned positive immunomodulator domains. . . . Other suitable candidates for the positive immunomodulator domain include the **interferons** (IFN).* (emphasis added).

The examiner's rejection is based on the premise that the working examples of the application are insufficient to support the breadth of the claims. However, it is not necessary for applicants to reduce to practice each and every possible permutation or embodiment described in their application in order to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. "Proof of enablement will be required for other members of the claimed *genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation*" (emphasis added). See Section 2164.02 of the MPEP. There is no undue experimentation associated with the use of any one of the well-characterized interleukin or interferon molecules instead of IL-2 in the inventive bi-functional molecule that is described extensively in applicants' working examples.

With respect to the latter, Section 2164.02 also states that "the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure" and that "*the absence of working examples [or evidence] will not by itself render the invention non-enabled*" (emphasis added).

If the examiner is to maintain this rejection then applicants respectfully request that the examiner, in accordance with Section 2164.02 of the MPEP, state why he "would not expect to be able to extrapolate that one example across the entire scope of the claims"; *i.e.*, applicants respectfully request that if the examiner maintains this rejection, then he must justify why he would not expect any interferon or any interleukin molecule, such as IFN-γ or IL-12, to

function as does the IL-2 in the bi-functional molecule and induce an immune response that is targeted to a specific cancer cell.

The examiner also states that the specification does not support a method of treating cancer using a truncated form or conservative variant of SEQ ID NO. 1. As outlined above, the present specification clearly details what is meant by the term "conservative variant" with respect to a receptor-antagonizing domain. The skilled artisan knows what kinds of amino acid substitutions can be made to a receptor-antagonizing domain, such as prolactin, that would not alter the desired function of that domain. In keeping with applicants statements above, applicants are not required to provide evidence for each and every possible conservative modification, truncation or combinations thereof, that could be made to SEQ ID NO. 1 in order to satisfy the enablement requirement.

For at least these reasons, applicants assert that the present claims are enabled and respectfully request that the examiner withdraw this rejection.

(iii) **Claims 1, 3, 4, and 5 are not anticipated**

The examiner believes that Lode *et al.* (supra) anticipates claims 1, 3, 4, and 5 because Lode *et al.* allegedly teaches a method of treating tumors using a protein containing an antagonizing domain and an immunomodulator region. Applicants disagree and traverse the rejection.

Lode *et al.* does not teach a bi-functional protein that induces apoptosis and directs the host's immune system to targeted cancer cells. Instead, Lode *et al.* combines a tumor vasculature-specific antiangiogenic integrin $\alpha_v$ with a tumor-specific antibody/IL-2 fusion protein to inhibit angiogenesis and provoke an immune response. "The simultaneous targeting of the vascular and tumor compartments proved very effective, because it combines ***a decrease in tumor cell nourishment*** with the active destruction of tumor cells" (emphasis added). See the second column at page 1595.

The present invention does not use a protein antagonist that decreases nourishment flow to tumor cells. Indeed, the antiangiogenic integrin $\alpha_v$ protein targets the machinery involved in angiogenesis, not cancer cells directly. For instance, Lode *et al.* state that "[A]ngiogenesis is characterized by invasion, migration, and proliferation of endothelial cells, processes that depend on cell interactions with extracellular matrix components. In this context, ***the endothelial adhesion receptor, integrin*** $\alpha_v\beta_3$ was shown to be a key player by providing a vasculature-specific target for antiangiogenic treatment strategies," (emphasis added).

Lode *et al.* conclude that "a peptide antagonist targeting the vasculature through interaction with $\alpha_v$ integrins ***expressed on angiogenic blood vessels*** suppressed blood vessel formation," (emphasis added). See the Discussion at page 1593. Moreover, product literature posted on Ancell Immunology Research Products website states that "[T]he alpha v beta 3 integrin complex binds vitronectin at the RGD sequence and also can bind to fibrinogen, von Willebrand factor, thrombospondin, fibronectin, osteopontin and collagen." See Appendix 1. Lode *et al.* does not state that a mutated $\alpha_v$ integrin be used to perform the antiangionenic function prescribed to the "antagonist."

Clearly, the integrin $\alpha_v$ antagonist of Lode *et al.* does not fall under the present invention's definition of a "receptor-antagonizing domain." As stated above, having read the specification, the skilled artisan would know that a receptor-antagonizing domain of the present invention is one that targets a receptor ***expressed on a cancer cell***, not one that is expressed on endothelial cells. Furthermore, in the case of prolactin and other growth hormones, mutation of glycine at position 129 renders the mutant a "receptor-antagonizing domain," because that residue is important in eliciting a wild-type effect of prolactin binding to a prolactin receptor.

Lode *et al.* describes the effects of the integrin molecule on inducing *vasularization*, not on inducing apoptosis. ("mice receiving the integrin $\alpha_v$ antagonist showed a 50% decrease in vascularization," Lode *et al.*, p.1592,

second column). Furthermore, Lode *et al.* state that the integrin $\alpha_v$ antagonist "was directed primarily to $\alpha_v\beta_3$" but that it also bound to $\alpha_v\beta_5$. See page 1594, first column. Such inconsistency clearly does not suggest that the integrin $\alpha_v$ antagonist could be used to directly target a cancerous cell as taught by applicants' invention. Indeed, Lode *et al.* state that "[H]owever, the effect of this integrin antagonist *clearly* ***was restricted to the tumor vasculature***," and that another molecule, *i.e.*, the "tumor compartment" of the treatment, was necessary for targeting destruction of cancer cells. See page 1594, second column and page 1595, first column. In addition, Lode *et al.* say nothing of the use of an integrin-based molecule to treat breast or prostate cancer. Lode *et al.* only says that a reduction in vasculature and the effects of a "tumor compartment" resulted in "tumor necrosis."

It is clear that then that in no way does Lode *et al.* anticipate the present claims, because Lode *et al.* does not teach a "receptor-antagonizing domain" of the present invention.

Accordingly, applicants respectfully request that the examiner withdraw this rejection.

The examiner also rejected claim 5 as being anticipated by Gillies *et al* (supra). The examiner states that Gillies *et al.* discloses an "antibody that binds to a receptor," interpreting that to mean that such an antibody is a "receptor-antagonizing domain" of the present invention. Claim 5 is specifically rejected because it recites that the positive immunomodulator domain of claim 1 is IL-12 and Gillies *et al.* teaches an IL-12-antibody fusion protein.

Contrary to the examiner's reasoning, the antibody of Gillies *et al.* is not a receptor-antagonizing domain. Gillies *et al.* state in column one of page 6195 that previous studies "utilized Abs [antibodies] specific for Ags [antigens] on melanoma and neuroblastoma cells." The antibody described does not alter or inhibit a particular function associated with a cell that expresses the antigen to which the antibody. In fact, Gillies *et al.* simply fused the IL-12 to "the carboxy

terminus of the Fc fragment of human IgG1." See the results section at page 6196.

(iv) **Claim 24 is not obvious over the cited prior art**

The examiner asserts that claim 24 is obvious over the combination of Lode *et al.* in view of Bulfone-Paus *et al.* (supra). Bulfone-Paus *et al.* was published after the filing date of the priority document to which the present application claims priority and therefore is not available as prior art. The publication date of Bulfone-Paus *et al.* is April 15, 2000. The present application was filed on March 23, 2001, but claims priority back to March 23, 2000.

Accordingly, the examiner's rejection is moot.

## IV. Conclusion

Applicants consider this application in suitable condition for allowance and earnestly seek the same from the examiner. Nevertheless, should there be any questions regarding the application, or if the examiner feels that a phone interview would expedite prosecution, the examiner is invited to contact the undersigned representative at the local telephone number below.

Respectfully submitted,

Date 14 Nov. 2002

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## MARKED-UP VERSION OF THE CLAIMS

1. (Once amended) A method for treating cancer, comprising administering to a patient that has cancer [an effective amount of] a protein that comprises [having] a receptor-antagonizing domain and a positive immunomodulator domain.

2. (Once amended) The [A] method according to claim 1, wherein the receptor-antagonizing domain is a prolactin-antagonist domain.

3. (Once amended) The [A] method according to claim 1, wherein the positive immunomodulator domain is an interleukin.

4. (Once amended) The [A] method according to claim 3, wherein the interleukin is an [interleukin 2 (]IL-2[)]

5. (Once amended) The [A] method according to claim 3, wherein the positive immunomodulator domain is an [interleukin 12 (]IL-12[)].

6. (Once amended) The [A] method according to claim 3, wherein the positive immunomodulator domain is [gamma interferon (]IFNγ)].

7. (Once amended) The [A] method according to claim 1, wherein the protein is a prolactin antagonist-interleukin 2 [(hPRLA-IL-2)] fusion protein.

8. (Once amended) The [A] method according to claim 2, wherein the prolactin-antagonist domain has [is characterized by a single amino acid substitute from Glycine to ] an a[A]rginine at position [corresponding to] 129 of the prolactin protein.

9. (Once amended) The [A] method according to claim 2, wherein the prolactin-antagonist domain comprises a protein comprising [having] the amino acid sequence of SEQ ID NO.[: 0]1 [(hPRLA) or a conservative variant thereof].

10. (Once amended) The [A] method according to claim 2, wherein the prolactin-antagonist domain comprises a truncated [truncation of a native] prolactin sequence [or a conservative variant thereof].

22. (Once amended) The [A] method according to claim 1 [3], wherein cells of the cancer [is characterized as] overexpress [expressing] a prolactin receptor at levels greater than in normal, healthy cells.

24. (Once amended) The [A] method according to claim 1, wherein the receptor-antagonizing domain is an apoptosis-promoting domain.

25. (Once amended) The [A] method according to claim 24, wherein the apoptosis-promoting domain inhibits [functions by inhibiting] STAT3 phosphorylation in a [targeted] cell to which the apoptosis-promoting domain binds.